CBER Perspective On Aseptic Processing In Isolators

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Topics

- 2004 FDA Aseptic Guidance
- Example of Prior Approval Supplement for Isolators
- Consideration for Isolators/CBER Prospective
- Inspection/Review issues

2004 Aseptic Guidance provides encouragement for isolators

Isolators “Offer tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing.”

CBER Review Approach

CBER/CDER Review approaches and expectations are basically the same.

Main differences:

- ORA Field investigators will conduct the PAI for CDER
- CBER reviewer/Inspector will conduct the PAI
- Product Type e.g. cell gene therapy

Example of Prior Approval Supplement

- **Supplement for new isolator vial filling line**

  In new vaccine filling facility
- **Supporting information:**
  - **Overview of facility including isolator filling suite and major systems in facility**
  - **Sterility assurance and contamination control**
  - **Qualification of the filling isolator**
  - **Validation of manufacturing processes and equipment (including computer validation)**
  - **CMC/product data**

Example of Prior Approval Supplement

Sterilization information provided:

- **Temperature mapping**
- **H_2O_2 distribution**
- **Flow rate**
- **Injection rate**
- **Capacity**
- **Aeration time**
- **H_2O_2 residues**
- **Media growth property**
- **Environmental testing at rest and in operation**

Example of Prior Approval Supplement

- **Two particle monitoring systems perform continuous monitoring of non-viable particulates in the isolator**
- **Media-fills were performed to validate the assurance of sterility of isolator filling operations**
- **Media fill were performed for initial qualification, semiannual requlification and after each major modification/renovation**

Example of Prior Approval Supplement

- **Validation of the cleaning method for the filling manifold**
- **Qualification of vial washer/sterilizer**
- **Validation of CIP/SIP of the transfer tubes of the stopper transfer station**
- **Qualification of capper in filling facility**
- **Qualification of autoclave**
- **Qualification of automatic inspection equipment**

Consideration for Isolators /CBER Prospective

Isolator Cleaning

Important for biologics - some products require special attention such as inactivation of live vaccine

- demonstrate inactivation and removal
- validation of H_2O_2 cycle after inactivation and cleaning

Decontamination

- Decontamination frequency should be justified
- Revalidation of decontamination cycle– minimum annually
- Breach in integrity should lead to decontamination of isolator
  - Power failure, valve failure, leaks
  - Should be investigated

Decontamination

- BI – appropriate numbers /certified /hard to reach locations
- Four to six-log reduction of challenge BI (target)
  - A four log reduction for controlled low bioburden materials in a transfer isolator
  - Uniformity of agent distribution should be evaluated
- Direct product contact surfaces should be ***sterilized***
  - Steam Sterilize: (anything that can be)
    - complete product pathway
    - Aseptic processing equipment or ancillary supplies (portable tools, implements, containers, etc.)
- At least six-log reduction is needed when used to render product contact surfaces free of viable organisms

Decontamination

The total-kill analysis is recommended method. The fraction-negative studies may be less accurate because the volume of space and airflow within an isolator may cause variable chemical exposure to isolator surfaces, depending on their position inside the unit.

Mouse hole

Our concern

- “Mouse hole” or exit port opens the isolator to the outside environment
- Represents a potential route of contamination
- Need Sufficient overpressure to ensure isolation
- Over pressure monitored on a continuous basis

Materials of construction

- Rounded corners, smooth, cleanable surfaces
- Avoid creating any occluded surfaces
- Use sanitary valves
- If drains necessary, good drain location & design
- Rigid wall construction of stainless steel and glass is common

HVAC System

- Maintained/monitored – temperature, differential pressure, humidity
- HEPA filters- certified
- Positive Pressure
  - Demonstrate isolation at minimum allowable pressure, continuous monitoring
  - Local Class 100 (ISO 5) zones at openings may be necessary

HVAC

- Positive air pressure adequate to separate internal from external environment
  - Dependent on the design of the isolator
  - Differentials of from 17.5 – 50 Pascals (0.07” – 0.2” water gauge) common
  - Air balance between the isolator and direct interfaces (e.g. dry heat tunnel) should be qualified

Air Flow

- Open isolators employ unidirectional air flow
  - Passes over critical area once and is exhausted from the isolator
- Turbulent air flow may be acceptable within closed isolators
  - Usually compact in size
  - Do not house processing lines

Classification

- Interior of Isolator - Class 100 (ISO 5) (dynamic) standards or better
- Environment surrounding the Isolator - Class 100,000 (ISO 8) (dynamic) or better
  - Higher (cleaner) background classification may be needed in some manufacturing situations
    - Design of the interfaces
    - Number of transfers in and out
- Aseptic processing isolator should not be located in an unclassified room

Environmental Monitoring

- Program should be established to monitor microbiological
  - Air quality
    - Periodically during each shift
  - Surface quality
    - Media cleaned off after sampling
  - Gloves or half suits
  - Non - viable particulate levels
    - At exit ports
  - Nutrient media not exposed to decontamination residues

Environmental Monitoring

- Monitoring Location – critical sites, product contact and processing gloves
- Deviation- investigated , implemented corrective actions

Preventive Maintenance Program

Well defined maintenance and calibration programs

- Critical instrument/equipment – appropriately calibrated
- Isolators monitored for leaks
- Alarm system – maintained and periodically challenged
- Alarm events – evaluated, investigated, documented as they occur
- Daily attention to integrity of gloves, half-suits, seams
- Transfer systems - gaskets, seals
- Defined replacement frequencies before breakdown

Transfer System

Transfer system- seal and gaskets designed not to compromise isolators integrity/sterility

Gloves

- Ergonomic placement of glove ports
- Access gloves and half suits – durable and flexible materials
- Breach in glove Integrity
  - A major potential weakness
    - Choice of durable glove material important
    - Visually evaluated for macroscopic defects at each use
    - Physical integrity test performed routinely
  - Integrating the use of a second pair of thin gloves on hands

Personnel

- Appropriately trained
- Aware of potential leaks in gloves and half suites, take necessary steps
- Use sanitized gloves as insurance against pinhole leaks
- Appropriate gowning level/practices defined
- Aseptic processing techniques remain critical
  - Use of sterile tools for manipulations

Media fill

- MF validated initially and repeated periodically, after critical changes
- Simulate worst case processing conditions
- Contaminated units thoroughly investigated/documented
- Rejected units properly justified/documented

Inspection/Review Issues…

Studies failed to demonstrate the ability to consistently produce a sterile product. Our findings indicate an unacceptable risk of microbiological contamination for commercial production lots (3 consecutive media fill failures). The barrier filling line lacks basic controls to ensure production of sterile product.

Inspection/Review Issues…

- **A large number of vials and over-wrap material accumulated in the bottom of the isolator at the vial in-feed staging area.**
  - **The affect of this material on the isolator operating dynamics has not been evaluated.**
  - **Limits on the amount of material that can accumulate without compromising the performance of the isolator have not been established.**

Inspection/Review Issues…

No method to remove accumulated empty vials from inside isolator after a five-day filling operation. Vials blocked air return grills.

Inspection/Review Issues…

- **A HEPA filter certification of the aseptic filling isolator due in December of 200X was not performed as required by a modification in the frequency schedule for filter certification**
- **Paper edged HEPA filters installed, which deteriorated after several VHP sterilizations cycle**

Inspection/Review Issues…

Regarding design of the syringe filling isolator:

There is a lack of assurance that HEPA filtered air is laminar across all work surfaces. Air returns are located approximately 3 inches from the work surface for most of the unit. However, one section of the isolator (near the filling pumps) that is approximately three feet wide has air returns are approximately 12 inches above the above the work surface. **Smoke studies simulating activities in the area show the air moving out before reaching the work surface where the operator was assembling the pumps. Further, OOS results have previously been found on various gloves within the unit.**

Inspection/Review Issues…

Excursions in the non-viable particulate counts were observed in the isolator during filling operations. There was no documentation of an investigation.

Inspection/Review Issues…

The makeup air to the cool zone of the depyrogenation tunnel from the vial staging area of the isolator is never monitored for quality.

Inspection/Review Issues…

Air flow through the exit mouse hole has not been assessed at the lowest operating parameters for the ability to preclude the introduction of contaminants into the isolator. Additionally, the correlation between the isolator overpressure and the exit mouse hole air dynamics has not been evaluated.

Inspection/Review Issues…

- **Review of video of a smoke study for the syringe isolator revealed that there is high turbulence in some areas of the unit.**
- **Smoke studies in the isolator were not performed under production parameters including production line speeds**

Inspection/Review Issues…

There was no validation study of the DPTE (double transfer door containers) containers to support a 2-month hold time after autoclaving

Inspection/Review Issues…

During the VHP surface sterilization cycle, the internal pressure of the isolator was observed to be set at 150 PA; whereas the approved VHP cycle validation report specified 100 Pa for this parameter

Inspection/Review Issues…

Please submit the final summary report for the validation for the validation of VHP. This report should include the rational for the routine cycle including all established parameters such as injection rate, isolator temperature and humidity, the claimed sterility assurance level, and minimum cycle duration.

Inspection/Review Issues…

- **The firm has not qualified the decontamination of the filling line carrier belt within the barrier.**
- **A black residue was observed on several gloves after cleaning.**
  - **Firm did not investigate the source of this residue.**
- **The IQ/OQ Protocol for the Barrier CIP cycle fails to objectively define the acceptance criteria.**
  - **The process did not clean riboflavin as specified in the protocol.**

Inspection/Review Issues…

The biological indicator used in validation studies was labeled by the manufacturer to have a population of 1.5×10^5 spores per strip. Please provide data that verify the labeled population of the biological indicator.

Inspection/Review Issues…

- **Re-qualification of the Syringe Filling Isolator failed because at the end of the VHP sanitization process 3 biological indicators showed signs of growth of the indicator organism (*Geobacillus stearothermophilus*).**
  - **The firm was unable to find a definitive cause (assumption was that tape covered the BI and did not allow for gas to come into contact with BI) for the lack of complete sanitization of the isolator. Neither the SOP nor the protocol for the validation specified corrective action for the failure. The firm did not successfully perform the complete validation but rather performed an investigation of the failure which included an abbreviated test of the failing locations only.**

Inspection/Review Issues…

Decontamination cycle study did not evaluate the actual production parameters. Validation runs were conducted at levels often exceeding the proposed hydrogen peroxide concentration set point by as much as 30-90 %

Inspection/Review Issues…

- **Multiple torn gloves were "tied-off" upon detection of tear defects during the course of production runs.**
- **A tear in a glove was not detected until the day following the fill.**
- **Processing was allowed to continue despite breaches in the isolator's integrity.**

Inspection/Review Issues…

- **Regarding the ultraviolet light transfer port:**
  - **The laminar flow air shower at the UV transfer port is classified at the Class 100,000 level.**
  - **The method used to transfer sterilized, depyrogenated vial stoppers into the UV transfer port could introduce contaminants.**
  - **there is no routine monitoring of the UV light intensity in the UV transfer port and no preventive maintenance schedule for this port.**

Inspection/Review Issues…

Procedures regarding aborting and rejecting any batch subjected to unacceptable conditions in the course of production were not complete.

Inspection/Review Issues…

One operator was observed placing his arm in the glove (on the outside of the enclosure) to perform an operation on the inside of the enclosure. He appeared to have difficulty getting his hand into the glove and was observed vigorously moving his gloved arm over empty vials as they moved around on the accumulation table. There is no procedure to give operators instructions on donning the gauntlet gloves and no instructions on appropriate movement in either the vial filling area or the syringe filling isolator.

Summary

- CBER/CDER Review approaches and expectations are the same
- Aseptic processing techniques and cGMP remain critical
- 2004 Aseptic Guidance provides encouragement to use isolators

Thanks…

For their contribution for this presentation:

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Question?

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